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Property-Based Selection of Membrane Permeable Macrocyclic Scaffolds in a DNA-Encoded Library

1200 **SURFACES** Binding Site Surface Area (Ų) **Biologics Protein-Protein Interactions** 1000 proteins + antibodies Н 800 Me HN N bRo5 GROOVES macrocycles + 600 ŃМе + natural products **CLEFTS** 400 Ro5 ŃМе small N Me 200 POCKETS molecules Ĥ 500 1000 1500 2000 Molecular Weight (Da)



Grant Koch

Griselimycin, %F=48



Able to make many different peptides at once ~ **10^12 libraries**

DNA encoded peptides – "Chemical barcoding"





Figure 1. DNA-encoded chemical libraries (DECLs). A) Generic structure of a DECL. B) Schematic representation of screening protocol.



GSK2256294, sEH inhibitor

Drugs must have:

- Bioactivity
- Metabolic stability
- Cell permeability







__`\$<mark>i-O-\$i</mark>-OH

,_`Šį́-**O**

-si-0-

Tightly packed column



HPLC separates mixtures of compounds based on their physical properties

- Si-O-Si⁻O O O - Si-O-Si-OH O O - Si-O-Si-O-Si O O - Si-O-Si-OH O O O Si-O-Si-OH 16 ⁻Si[/]-O-Si_{-O} O O -Si[/]-O-Si_{-OH} *1*6 Deng, et al., ACS Med. Chem. Lett., 2015





